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(54) Title: ANTI-VAGINITIS COMPOSITION FOR TOPICAL USE COMPRISING ONE OR MORE ANTI-VAGINITIS MEDICAMENTS AND ONE OR MORE LOCAL ANAESTHETICS

(57) Abstract

A pharmaceutical composition for topical administration in the treatment of vaginitis comprising one or more anti-vaginitis medicaments such as metronidazole and miconazole and one or more local anaesthetics such as lidocaine or benzocaine.

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ANTI-VAGINITIS COMPOSITION FOR TOPICAL USE COMPRISING ONE OR MORE ANTI-VAGINITIS MEDICAMENTS AND ONE OR MORE LOCAL ANAESTHETICS

This invention concerns novel pharmaceutical compositions for combating vaginal infections.

Vaginitis is most often caused by infection with candida albicans, trichomonas vaginalis or gardnerella sp, either singly or mixed. Derivatives of imidazole and nitroimidazole are often used to treat such conditions and other types of drugs used include nitrofurfuryl derivatives and various antibiotics.

The active ingredients may be formulated for either oral or topical administration. Metronidazole for example is often administered by the oral route, but mixed infections cannot be treated satisfactorily in this way and compositions for topical administration, particularly pessaries, containing two or more active ingredients are more suitable for this purpose. Topical formulations containing only a single active ingredient are also used.

It has been found in the past that the topical application of the active ingredients has sometimes been accompanied by local irritation but this has generally been acceptable to patients. We have now found that increased and unacceptable irritation by stinging and burning occurs in some circumstances, particularly when a combination of two or more active ingredients is used. Increased irritation can be caused for example when miconazole is used, particularly in the presence of a second active ingredient such as metronidazole. We have further found that the soreness caused by vaginitis can be alleviated while at the same time reducing or eliminating this irritation by including a local anaesthetic in the composition.

The invention thus provides a pharmaceutical composition for topical administration in the treatment

of vaginitis comprising one or more anti-vaginitis medicaments and one or more local anaesthetics.

The composition should include at least one medicament active against trichomonas vaginalis, preferably metronidazole, and it is desirable to include one or more drugs active against candida albicans and/or gardnerella sp. as the administration of metronidazole alone sometimes results in proliferation of infecting fungal pathogens. A fungicidally active derivative of nitroimdazole such as butoconazole or, more preferably, miconazole, is advantageously used as the drug active against candida albicans. Ornidazole, ketoconazole, tioconazole and tinidazole are also suitable fungicidally active agents. Where metronidazole is used as the anti-trichomonal drug, it will also be effective against gardnerella sp. The invention is particularly concerned with the use of metronidazole and miconazole as a local anaesthetic is very effective in increasing the acceptability of this combination of active ingredients.

The local anaesthetic may for example be an amide-type anaesthetic such as aptocaine, bupivacaine, butanilicaine, carticaine, cinchocaine, clibucaine, ethyl parapiperidinoacetyl-aminobenzoate, etidocaine, lidocaine (lignocaine), mepivacaine, oxethazaine, prilocaine, pyrrocaine, ropivacaine, tolycaine or vadocaine, or a mixture thereof such as lidocaine and prilocaine. Anaesthetics of the p-aminobenzoic acid ester type such as benzocaine may also be used. The anaesthetic may also be used in the form of a salt.

The local anaesthetic may be used in an amount of 0.1-10.0% by weight, preferably 1.0-7.0%. The local anaesthetic is preferably lidocaine and may be used in the form of its free base (for example in the an amount of 1.0-3.0%, by weight, preferably about 1.5%) or a salt such as its hydrochloride, for example 1.5-4.0% by weight, preferably about 2%. The use of the anaesthetic

at these low concentrations results in the compositions being well tolerated.

The composition may be in the form of a cream containing the anti-vaginitis medicament(s) together with one or more local anaesthetics. A conventional cream base may be used, e.g. containing oily or waxy materials such as liquid paraffin, white petroleum or cetyl alcohol, water and one or more surfactants to produce a water-in-oil emulsion. A bactericide such as benzalkonium chloride is conveniently present.

Preferably, the compositions take the form of pessaries comprising a pessary base containing the anti-vaginitis medicament(s) and one or more local anaesthetics.

The pessary base may be of any conventional material for vaginal administration such as glycerol/gelatin glyco-gelatin, macrogols (polyethylene glycols), natural, synthetic or semisynthetic hard fats, and fractionated palm kernel oil. A particularly preferred material is a hard fat such as cocoa butter (theobroma oil), for instance the range of cocoa butter-based products sold under the trade name Witepsol by Dynamit Nobel, Slough, England.

The pessary base preferably contains a surfactant to promote dispersal of the active substances and give continuous penetration of the active substances into the mucosal folds.

The surfactant may be a cationic, non-ionic, anionic or amphoteric surfactant although non-ionic surfactants are preferred. Anionic surfactants include salts of long chain alkyl sulphonate esters such as sodium lauryl sulphate, sodium cetostearyl sulphate and sodium tetradecyl sulphate; salts of long chain carboxylic acids such as stearates.

Cationic surfactants include quaternary ammonium or pyridinium compounds such as benzalkonium chloride (a mixture of benzyl alkyl dimethyl chlorides, the alkyl

chain ranging from C_8 to C_{18}), tetradecyltrimethyl ammonium bromide and cetylpyridinium chloride.

Amphoteric surfactants include lauryl 1-carboxy glycine and lecithins such as soya lecithin.

Non-ionic surfactants include glycol and glycerol esters such as glyceryl monostearate; macrogol esters and ethers such as cetomacrogol; sorbitan and mannitan esters such as sorbitan tristearate; and polyoxyethylene derivatives of such sorbitan esters, for instance polyoxyethylene (20) sorbitan mono-oleate.

The level of surfactant required in the pessary formulation will be readily determined by those skilled in the art and will depend on the specific surfactant and the nature of the pessary base; conveniently it is in the range 0.1 to 10 percent by weight, preferably 1 to 5 percent.

It is especially preferred to use a cetomacrogol surfactant in conjunction with a cocoa-butter base such as Witepsol. In such a formulation the surfactant is suitably present in the range 1 to 5 per cent by weight, for instance about 40mg in an overall pessary weight of 2540mg (including active ingredients).

A broad spectrum antibiotic such as pivampicillin or clindamycin may advantageously also be included. In order to counter the inflammation and itching associated with vaginitis, it may be beneficial to include an antiinflammatory drug such as hydrocortisone. Lactic acid may also advantageously be included as a further active ingredient. The compositions may also include chlorophyll as a deodorant.

The quantity of metronidazole is conveniently from 250 to 1500 mg per pessary, more preferably from 400 to 1200 mg and suitably about 500 mg.

The pessary may contain from 50 to 600 mg of miconazole, preferably from 50 to 450 mg and typically 100 mg. The miconazole may be in the form of the free base or as a salt, for instance the nitrate, especially

in the pessary base.

The compositions may be formulated for rapid or delayed (sustained) release, or preferably both, of the active ingredient(s) and/or the local anaesthetic(s). Any suitable method may be used to provide delayed release of these substances.

In a preferred system, delayed release may be achieved by using a local anaesthetic in two or more different forms having different solubilities, for example in hydrophobic and hydrophilic forms. For example, an anaesthetic such as lidocaine in free base form is practically insoluble in water but soluble in lipids, whereas a salt (e.g. the hydrochloride of an anaesthetic such as lidocaine) is very soluble in water but less soluble in lipids. On account of its hydrophilicity a salt is released rapidly from the pessary or cream base, whereas the free base is only released slowly because of its lipophilicity, thus providing prolonged anaesthetic action. The inclusion of both the salt and the free base can therefore give differing rates of release of the anaesthetic, thus providing both immediate and sustained action.

Such compositions can for example contain 0.1-3.5% (preferably about 2.0%) by weight of lidocaine HCl and 0.1-3.0% (preferably about 1.5%) by weight of lidocaine.

The total amount of lidocaine and its hydrochloride is preferably not more than 5% by weight. The relative amounts of the free base and the salt used can be varied depending on the nature of the pessary or cream base, in particular according to the lipophilic and hydrophilic properties of the base. However in general the composition can contain 20-80% of the free base form of the anaesthetic and 80-20% of the salt form, on the basis of the total weight of the two forms.

A lidocaine salt such as the hydrochloride can be included in a pessary base (e.g. a cocoa butter-based material) as a suspension or, preferably, dissolved in

the base with the aid of a surfactant (particularly a non-ionic surfactant such as referred to above). The free base can be dissolved directly in the pessary base.

Similar techniques can be used to include the anaesthetics in a cream formulation. Thus the salt form can be mixed with the aqueous phase ingredients of the cream and the free base form with the oily phase ingredients. The two phases can then be mixed together to form a cream emulsion containing the two forms of the anaesthetic in the different phases. Since it is possible to vary the lipophilicity of the oil phase, the release rate of the lidocaine from this phase can therefore be adjusted to enable a slow but continuous release of lidocaine from the oil phase. Conversely, the hydrophilicity and the pH of the aqueous phase can be changed to vary the release of lidocaine from the aqueous phase. In this manner it is possible to tailor the release rate profiles of lidocaine from the two phases so that they complement each other, resulting in prolonged release of lidocaine from the cream base containing the emulsion of the two phases.

Other methods may also be used to provide both rapid and delayed release. For example, the composition may include a cream or pessary base containing one or more active ingredients and one or more local anaesthetics for rapid release and porous particles dispersed therein for delayed release of one or more local anaesthetics and preferably also one or more active ingredients over a prolonged period, for example 24 hours. The anaesthetic(s) may thus be included in the cream and pessary compositions described in WO 95/07071.

The use of anaesthetics having different solubilities may also be adopted in the formulations including porous particles described above, for example by including lidocaine hydrochloride in the porous particles and its free base in the continuous phase or vice versa.

The porous particles may contain two or more active ingredients and anaesthetics, and the composition may contain mixtures of porous particles each containing different active ingredients and anaesthetics or different mixtures thereof.

A wide range of porous particles are available, as described in WO88/01164, WO89/10132, US-A-4 873 091 and 4690825 and EP-A-306236, the contents of which are incorporated herein by reference.

In such porous particles, the total pore volume is preferably in the range 0.1 to 2.0 ml/g, more preferably 0.3 to 1.0 ml/g. The diameters of the particles will generally be in the range 1 to 1000 microns, preferably 5 to 100 microns, more preferably 10 to 50 microns. The surface area of the particles will generally range from about 1 to 500 m^2/g, preferably 20 to 200 m^2/g.

The porous particles may be composed of a wide range of materials. Many synthetic, organic polymers are suitable, as well as natural substances such as cellulose or gelatin. The choice of material will depend in part on the intended means of delayed release of the active medicament, i.e. diffusion, compression, dissolving or melting.

Where diffusion of the active medicament is intended, the porous particles may be relatively rigid. This has the advantage that the outermost pores do not collapse when the medicament diffuses out and thus do not block the diffusion of the medicament from the inner pores. Such rigidity can be controlled by the degree of cross-linking of polymeric materials of which the particles are composed. The degree of cross-linking will generally be at least 10%, more usually in the range 20 to 80%, for example 25 to 60%.

Polymers of which the particles may be formed include polyolefins, including polyethylene, polystyrene, polydicyclopentadiene etc.; polyacrylate esters, e.g. optionally alkoxylated C_{1-10} alkyl,

cycloalkyl, aryl or aralkyl esters of polyacrylic or polymethacrylic acids; polyvinyl esters e.g. polyvinyl acetate or polyvinyl laurate; polyvinyl ketones, e.g. polyvinylmethyl ketone; and polyvinyl ethers, e.g. polyvinylpropyl ether.

The porous particles in a cream may liberate the active medicament by diffusion, pressure, dissolving or melting. One preferred embodiment is that the particles are elastically compressable so that after first application of a cream whereby the medicament contacts the infected area, application of gentle pressure, for example by rubbing, causes rapid release of the active medicament to provide a coating of medicament over the layer of cream.

Elastically compressable particles may be composed of elastomers, such as those described in US-A 4 873 091, including for example, isoprene rubbers, butadiene rubbers, chloroprene rubbers, styrene butadiene. Particularly useful are ethylene-propylene-diene terpolymers, wherein the diene components may be straight chain diolefins, cyclic dienes and bicyclic dienes. Examples of such dienes include 1,4-hexadiene, dicyclopentadiene and ethylidene norbornene. Silicone rubbers may also be used.

Porous particles which dissolve, primarily in aqueous body fluids, may be composed of water-soluble gels including gelatin, agarose etc and certain polymethyl methacrylates such as Eudragit (Röhm, Darmstadt) which dissolve at the pH of the vagina.

Porous particles which melt may be composed of fats and waxes of the type used in suppositories which melt at body temperatures but which are solid at room temperature as well as gelatin.

Porous materials for use in compositions of the invention may be made in any convenient way. Thus, it is possible to polymerise one or more suitable monomers in the presence of a dispersed porogen: after

polymerisation, the porogen may be removed, e.g. by evaporation or solvent extraction, to provide a network of interconnected pores. The active ingredient or anaesthetics can then be absorbed into the porous material, if desired by first evacuating air from the pores. The active ingredient or anaesthetic can, however, itself be used as the porogen: the material may be dispersed in droplets through a monomer with which it is immiscible so that after polymerisation the active medicament effectively fills pores within the polymeric material. In general, however, it is preferred to prepare the porous material first in order to remove rigorously all traces of monomer, catalysts and cross-linking agents, before introduction of active ingredient or anaesthetic.

A number of possible methods of manufacture of porous material, in particular porous particles, are described in the patents listed above.

In general, porous particles may conveniently be produced by emulsion or suspension polymerisation in a liquid - liquid system. Thus, for example, a solution comprising the chosen water-immiscible monomer, any cross-linking agent required, a catalyst, if needed, and a porogen which is miscible with the solution but immiscible with water. The solution is then suspended in an aqueous solution, which may contain one or more suspending agents or surfactants and polymerisation is initiated e.g. by raising the temperature or by irradiation. The porogen is then removed from the solidified particles, e.g. by evaporation or extraction into a solvent which is substantially inert to the polymer.

Examples of such porogens include C_{5-12} alkanes, C_{5-8} cycloalkanes and aromatic solvents such as benzene toluene etc. The particles will normally be washed thoroughly to remove contaminants, using solvents such that the final solvent can be removed by evaporation.

In general, particle diameter may be controlled by the degree of agitation to prepare the initial emulsion. The pore diameter and pore volume are controlled by the amount of porogen used and the degree of cross-linking.

The monomers used to prepare the particles may be any of those appropriate to make the polymers set out above. Suitable cross-linking agents for mono-olefins include poly-ethylenically unsaturated monomers.

The dosage of active medicament(s) an anaesthetics contained in the porous particles will vary with the individual medicaments and their half-lives. In general, the ratio of delayed release medicament to rapid release medicament is preferably in the range 1:1 to 5:1, for example 2:1 to 4:1.

The porous particles may be evenly distributed throughout the composition or, in the case of pessaries, may be concentrated in one or more zones, for example in a core.

In general, the size of the porous particles is preferably such that they cannot be taken up into the lymph ducts. On the other hand, large particles give a gritty effect which may produce discomfort. In general, the preferred size range for the porous particles is 10-100 microns.

Delayed release of the active ingredient(s) and anaesthetic(s) may also be provided by using the Polytrap and Hydrosponge systems (both trade marks of Advanced Polymer Systems, Inc.). Porous polymeric beads which have a cationic surface charge may also be used, such as for example described in EP-A-0369741 and WO 93/07862.

The delayed release of the active ingrdient(s) and anaesthetic(s) may also be effected by including in the composition liposomes encapsulating these materials. Liposomes are vesicles of phospholipid membranes, and methods of preparing them are described for example in US-A-4937078, 4485054 and 4761288 which are incorporated

herein by reference. Thus the active ingredient(s) and anaesthetic(s) are dissolved or dispersed in a lipid-containing organic solvent. Phospholipids are particularly useful, such as phosphatidylcholines, lysophosphatidylcholines, phosphatidylserines, phosphatidylethanolamines and phosphatidylinositols. Such phospholipids may be modified with for example cholesterols, stearylamines and tocopherols. The solvent then is evaporated, typically under a reduced pressure, to yield a thin lipid film containing the active ingredient(s) and anaesthetic(s). The film is then hydrated, with agitation, using an aqueous phase containing any desired electrolyte, and lipid vesicles entrapping the active ingredient(s) and anaesthetic(s) are produced. In a similar manner, the active ingredient(s) and anaesthetic(s) can be included in lipospheres such as described in US-A-5227165. These lipospheres have average diameters of 0.35-250 microns and have cores containing the active ingredient(s) and anaesthetic(s) dispersed in an inert hydrophobic vehicle and having a phospholipid surface layer. The lipospheres can be prepared by forming a liquid of the core material, adding phospholipid to the core material, adding an aqueous solution to the mixture, and mixing until a suspension of lipospheres is formed.

Another system that can be used is to embed the active compound(s) and anaesthetic(s) between layers of lipid (e.g. monoglyceride) crystals by the Crystalip system (trade mark, Bioglan) as described for example in WO 93/20812.

A further method of providing delayed release of the active ingredient(s) and anaesthetic(s) is by the use of hollow pessaries containing these materials. The hollow pessaries can be formed by moulding the pessary material around central pins, introducing the active materials into the cavities and then filling the remainder of the cavities with more pessary base.

The pessaries may be presented in a pack to provide a complete course of treatment, with some of the pessaries containing the local anaesthetic for initial use (e.g. over the first three days) and some without the anaesthetic for use when the symptoms have begun to subside.

The following examples are given by way of illustration only:

Example 1

Pessary

Metronidazole	500.0mg
Miconazole nitrate	100.0mg
Lidocaine (1.5%)	37.5mg
Lidocaine hydrochloride (2.0%)	50.0mg
Witepsol W35	1762.5mg
Cetomacrogol	50.0mg
	2500.0mg per pessary

Alternatively, the composition can contain 2.0% lidocaine and 1.5% lidocaine hydrochloride.

Method of manufacture

The two active ingredients, the lidocaine and the surfactant of the base are mixed into the molten Witepsol W35 and the resulting mixture is poured into pre-cooled moulds. The moulds are passed through a cooling tunnel at -10°C, the pessaries are removed from the moulds and packaged. 0.1% by weight of chlorophyl may also be added to the base.

Example 2

Cream

	%
Liquid paraffin	23.75
White petrolatum	8.0
Cetyl alcohol	7.0
Span 60	3.0
Miconazole nitrate	2.0
Metronidazole	10.0
Lidocaine	1.5
Lidocaine hydrochloride	2.0

Potassium dihydrogen phosphate	0.5
1% Aqueous benzalkonium chloride	10.0
Tween 60	5.0
70% Aqueous sorbitol	5.0
Water	22.25
	100.0

Alternatively, the composition can contain 2.0% lidocaine and 1.5% lidocaine hydrochloride.

The oily phase comprising the liquid paraffin, white petrolatum, cetyl alcohol, lidocaine and Span 60 are mixed at 60°C. The aqueous phase comprising the remaining components is also blended at 60°C and the two phases combined and blended.

Example 3

One pessary contains

Metronidazole	500.0mg
Miconazole nitrate	100.0mg
Lidocaine	75.0mg (3%)
Lidocaine HCl	25.0mg (1%)
Witepsol W35	1750.0mg
Cetomacrogol	50.0mg
Total	2500.0mg

Preparation - as Example 1

Example 4

Cream:

	%
Liquid paraffin	23.75
White petrolatum	8.0
Cetyl alcohol	7.0
Span 60	3.0

Miconazole nitrate	2.0
Metronidazole	10.0
Lidocaine	3.0
Lidocaine HCl	1.0
Potassium dihydrogen phosphate	0.5
1% Aqueous benzalkonium chloride	10.0
Tween 60	5.0
70% Aqueous sorbitol	5.0
Water	21.75
Total	100.0

Preparation - as Example 2

Example 5

Pessary:

Metronidazole	500.0mg	
Micronazole	100.0mg	
Lidocaine	25.0mg	(1%)
Microsponges* with lidocaine (40% loaded)	250.0mg	(4%)
Witepsol W35	1,575.0mg	
Cetomacrogol	50.0mg	
Total	2,500.0mg	

* All held within polystyrene-divinylbenzene porous beads.

Preparation - as Example 1.

Example 6

Pessary:

Metronidazole	100.0mg	
Miconazole nitrate	20.0mg	
Lidocaine	35.0mg	(1%)
Microsponges* with metronidazole	1,250.0mg	(500mg

(40% loaded)	active)
Microsponges* with Miconazole	250.0mg (100mg
(40% loaded)	active)
Microsponges* with Lidocaine	350.0mg (4%)
(40% loaded)	
Cetomacrogol	70.0mg
Witepsol w35	1,425.0mg
Total	3,500.0mg

* All held within polystyrene-divinylbenzene porous beads

Preparation - as Example 1

Example 7

Pessary:

Metronidazole	500.0mg
Miconazole nitrate	100.0mg
Lidocaine	25.0mg (1%)
Lidocaine HCl	75.0mg (3%)
PEG 4000	1,073.0mg
PEG 1000	545.0mg
PEG 400	140.0mg
Monateric 951A	42.0mg
Total	2,500.0mg

Preparation - as Example 1

Monateric is a surfactant available from Mona Industries Ltd., Paterson, New Jersey, USA.

Example 8

Cream:

	%
Liquid paraffin	20.75
White petrolatum	8.0

Cetyl alcohol	7.0
Span 60	3.0
Miconazole nitrate	2.0
Metronidazole	10.0
Lidocaine HCl	1.0
Microsponge* entrapped lidocaine (40% loaded)	10.0 (4% active)
Potassium dihydrogen phosphate	0.5
1% Aqueous benzalkonium chloride	10.0
Tween 60	5.0
70% Aqueous sorbitol	5.0
Water	17.75
	100.0%

* All held within polysytrene-divinylbenzene porous beads.

The oily phase comprising the liquid paraffin, white petrolatum, cetyl alcohol, lidocaine and Span 60 are mixed at 60°C. The aqueous phase comprising the remaining components except the porous beads is also blended at 60°C and the two phases combined and blended. The porous beads are added subsequently and dispersed throughout the cream.

Example 9

Pessary:

Metronidazole	500.0mg
Miconazole nitrate	100.0mg
Lidocaine	50.0mg
Witepsol w35	1,800.0mg
Cetomacrogol	50.0mg
	2,500.0mg per pessary

Preparation - as Example 1.

Alternatively, the composition can be adjusted to contain 37.5mg lidocaine and 1812.5mg Witepsol.

Example 10

Cream:

	%
Liquid paraffin	24.75
White petrolatum	8.0
Cetyl alcohol	7.0
Span 60	3.0
Miconazole nitrate	2.0
Metronidazole	10.0
Lidocaine	4.0
Potassium dihydrogen phosphate	0.5
1% Aqueous benzalkonium chloride	10.0
Tween 60	5.0
70% Aqueous sorbitol	5.0
Water	20.75
	100.0

Preparation - as Example 2.

Alternatively, the composition can contain 1.5 or 2% lidocaine with corresponding increases in the amount of liquid paraffin.

Claims

1. A pharmaceutical composition for topical administration in the treatment of vaginitis comprising one or more anti-vaginitis medicaments and one or more local anaesthetics.

2. A composition according to claim 1 which is formulated for rapid or delayed (sustained) release, or both, of the said medicament(s) and/or the local anaesthetic(s).

3. A composition according to claim 2 in which rapid and delayed release of the local anaesthetic is provided by using the anaesthetic in both free base and salt form.

4. A composition according to claim 2 which comprises a cream or pessary base containing one or more of said medicaments and one or more local anaesthetics for rapid release and porous particles dispersed therein for delayed release of one or more local anaesthetics.

5. A composition according to any of claims 2 to 4 which includes porous particles for the delayed release of one or more of said medicaments.

6. A composition according to any preceding claim in which the said medicaments are metronidazole and miconazole.

7. A composition according to any preceding claim in which the local anaesthetic is lidocaine or benzocaine.

8. A composition according to any preceding claim which includes a surfactant.

9. A composition according to any preceding claim in the form of a pessary.

INTERNATIONAL SEARCH REPORT

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PCT/GB 97/01355

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 //(A61K31/415,31:215),(A61K31/415,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Vaginal candidosis (moniliasis)" DRUG THER.BULL., 1976, 14/19 (75-76), ENGLAND, XP002041929 see page 76 ---	1-9
A	NAIR M.K. ET AL: "Development of anticandidal delivery systems: (I) anticandidal activities of antifungal agents and synergistic combination with other drugs" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY,27-02-1996, 22/3 (237-242), USA, XP002041930 see page 211, column 1, paragraph 4 - column 2, paragraph 1 -----	1-9

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 1997	15. 10. 97

Name and mailing address of the ISA	Authorized officer
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